

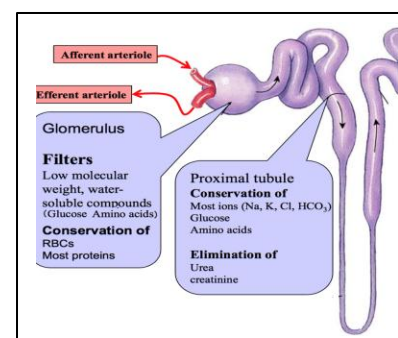
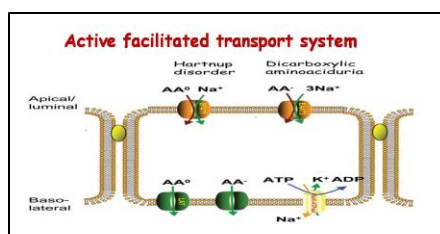
# Role of kidney in transport of amino acids and metabolic disorders affecting kidney

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By the end of this lecture the student will be able to:

1. Describe the role of kidney in amino acid transport.
2. Elaborate the biochemical aspects of Hartnup disease and other Inborn error of renal amino acids transport
3. Interpret the biochemical bases of Cystinuria and Cystinosis
4. Explain the Causes of Hyperoxaluria.

„ Amino acids are continuously filtered by the glomeruli & is reabsorbed by the renal tubules



„ Amino acids transport in kidney by two Mechanisms :

1- Active facilitated transport system

2- Gamma Glutamyl cycle (Glutathione transport system)

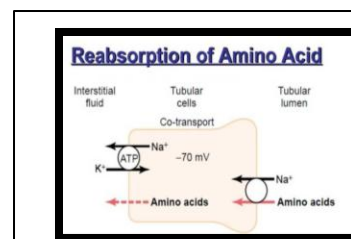
**Active facilitated transport system**

**Require protein carrier & ATP (energy dependent )**

For each group of AAs there is a specific protein carrier

e.g.

- ☐ Neutral amino acids (SMALL & LARGE )
- ☐ Basic amino acids and cystine
- ☐ Acidic amino acids
- ☐ Glycine and imino acids.



## Inborn error of renal amino acids transport

### 1- Hartnup disease

### 2- Iminoglycinuria

### 3- Cystinuria

#### 1- Hartnup disease

- „ Hartnup disease (also known as "pellagra-like dermatosis" )
- „ It is an autosomal recessive metabolic disorder
- „ There is impairment of intestinal absorption and renal reabsorption of neutral amino acids (including tryptophan)
- „ Pellagra like manifestations, aminoaciduria
- „ What is pellagra??

It is a disease that results from nicotinic acid (niacin) deficiency Causes:

- 1- Decrease tryptophan in diet. (Zein of maize)
- 2- Decrease tryptophan absorption (Hartnup disease ).
- 3- Pyridoxal-phosphate deficiency (plp).
- 4- Carcinoid tumour :( 60% of tryptophan is converted into serotonin

→ ↓ production of nicotinic acid.

#### Treatment:

- 1- Treatment of the cause.
- 2- Nicotinic acid supplement.

◆ Pellagra symptoms: 4 "D's"

- Diarrhea
- Dermatitis
- Dementia
- Death



## 2- Iminoglycinuria

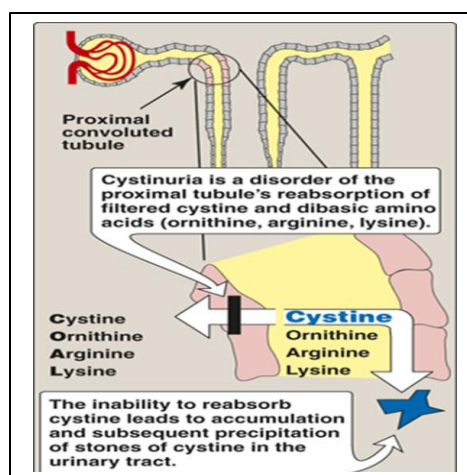
An inherited defect in renal tubular reabsorption of the amino acid glycine and the imino acids proline and hydroxyproline resulting in excess urinary excretion of all three amino acids.

## 3- Cystinuria

- It is the most common inborn error of amino acids transport
- About :1 in 7000 births
- It's an autosomal-recessive defect in the transport protein that is responsible for renal tubular reabsorption of cystine, ornithine, arginine and, lysine (COAL)by renal proximal tubules .
- The only manifestation of cystinuria is:
- cystine renal stones

### Pathophysiology of Cystinuria

- Normally Amino acids filtered undergo nearly complete reabsorption by proximal tubular cells.
- Only 0.4% of the filtered cystine appears in the urine.



- There are at least 2 transport systems are responsible for cysteine reabsorption:

**1-High-affinity system:** Mediates uptake of 10% of cystine and the dibasic amino acids at the third segment (S3) of the proximal tubule.

- Affected in persons with cystinuria.

**2-Low-affinity system:** This system is present in the (S1-S2) part of the proximal tubule, Responsible for 90% of cystine reabsorption

- Defective reabsorption causes elevated levels of dibasic amino acid secretion in the urine.
- Ornithine, lysine, and arginine are completely soluble.
- Cystine, which is not very soluble in the urine, forms renal calculi in the acidic pH of urine

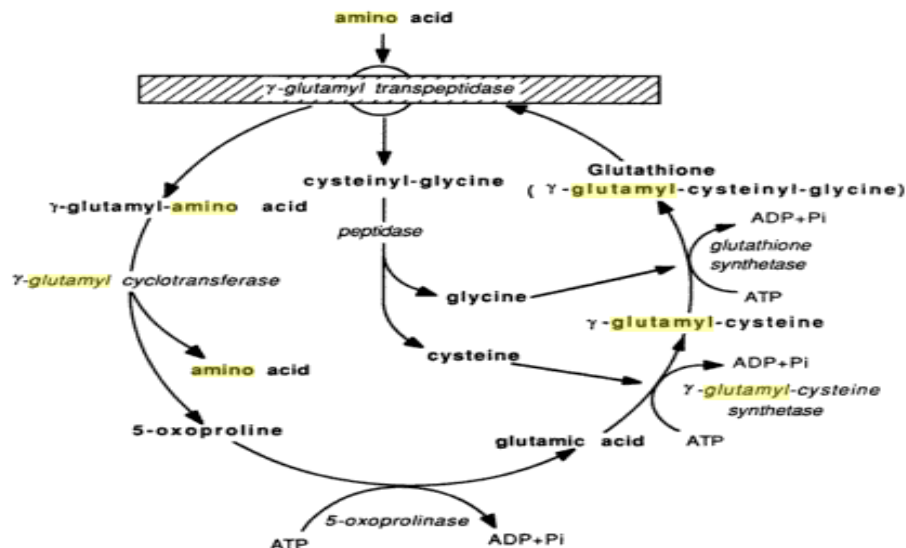
### **Cystinuria**

- Symptoms: Renal colic caused by cystine stones.
- Diagnosis:
  - Measurement of cystine excretion in the urine.
  - urine analysis: cystine crystals
- Treatment: increased fluid intake and alkalinization of the urine.

## The second mechanism for renal amino acids transport?

### Gamma Glutamyl cycle (Glutathione transport system)

- Active : In intestine, Kidney Tubules , Brain



$\gamma$  Glutamyl cycle Requires 3 ATP and 5 enzymes :

One is membrane bound { $\gamma$ -Glutamyl transpeptidase (GGT)} & 4 are cytosolic

#### Clinical significance of GGT?

It is a membrane bound, that is expressed also in the liver and biliary tract cells .

#### Elevated levels **occurs** in:

- 1)Biliary obstruction
- 2)cancer head of pancreas(pressure on the common bile duct)
- 3)Alcoholic liver disease (the enzyme is induced by alcohol intake).

## What is Oxoprolinuria?

- „ It is a metabolic error caused by a defect in 5-oxoprolinase enzyme
- „ It is characterized by accumulation of 5-oxoproline in blood and hence excreted in urine. It is associated with mental retardation.

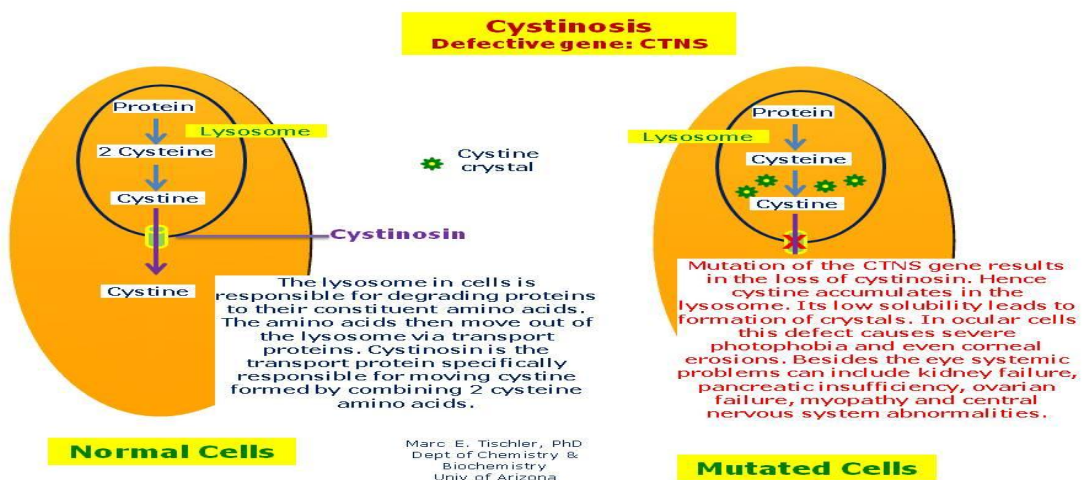


## Metabolic disorders affecting kidney

### 1- Cystinosis      2- Primary hyperoxaluria

#### Cystinosis

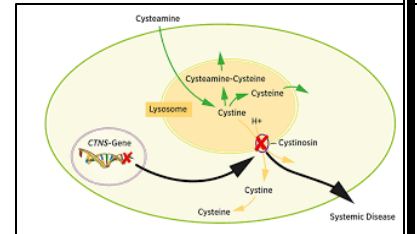
- 1- It is a rare disorder caused by a defective carrier that normally transports cystine across the lysosomal membrane from lysosomal vesicles to the cytosol.
- 2- Cystine accumulates in the lysosomes in many tissues and forms crystals & cause tissue damage especially in the kidneys and eyes.



**Symptomatic ttt:**

- Free access to water
- Replacement of urine loss due to renal Fanconi syndrome
- Hormone replacement when required

**Specific ttt with Cysteamine**



## 2. Hyperoxaluria

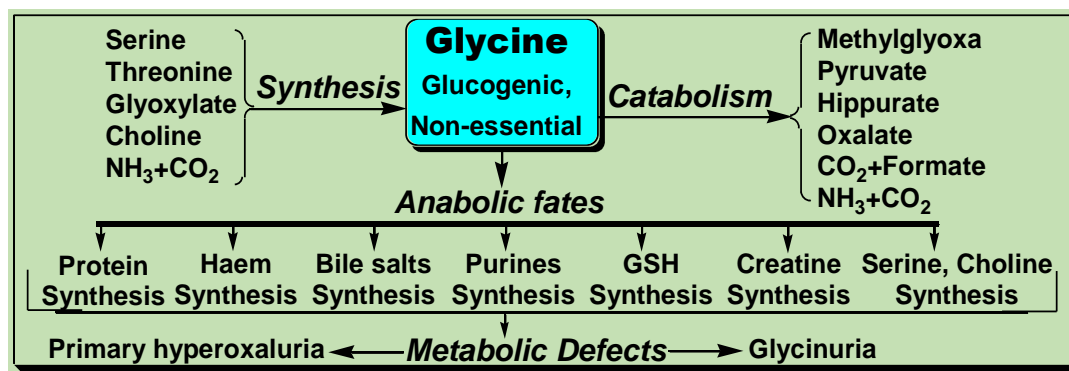
**Favors formation of calcium oxalates stones**

**causes:**

1- primary: primary hyperoxaluria.

2- Secondary: increase intake of diet rich in oxalate like chocolate, coffee, tea,

Soda, and spinach

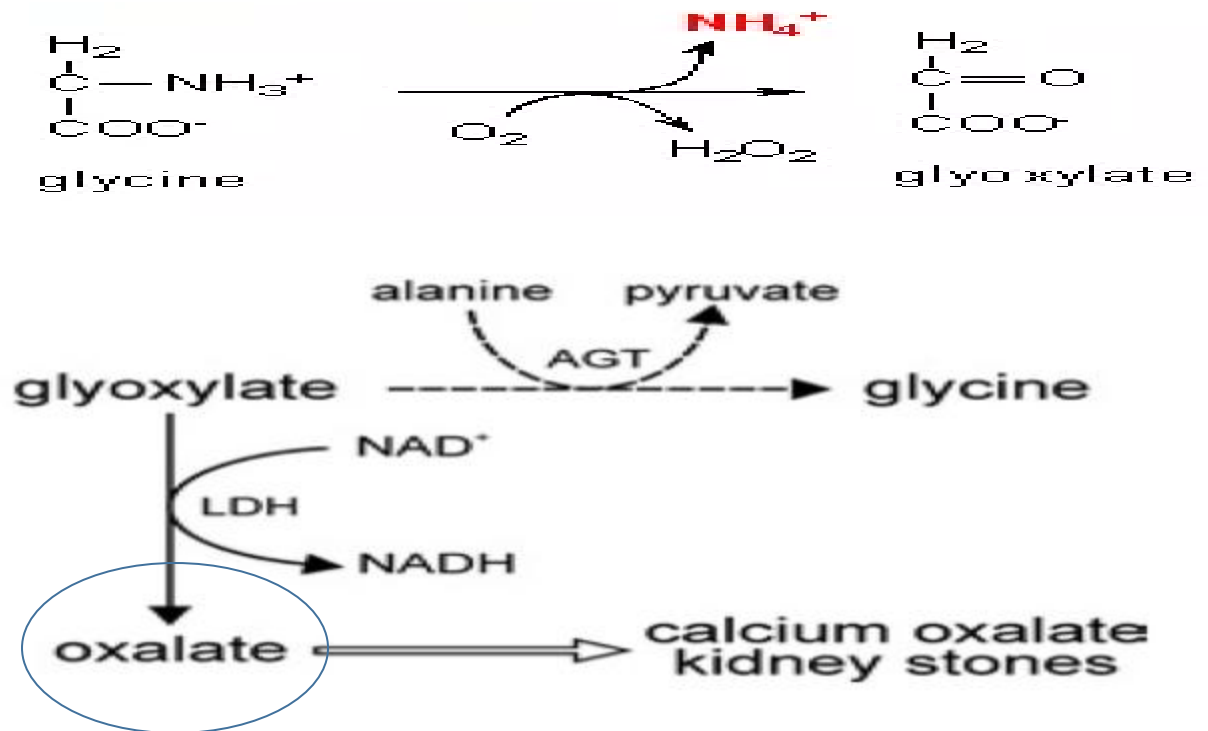


## Primary hyperoxaluria

- Glycine can be deaminated to glyoxylate, which can be:
  - Transaminated to glycine by Glycine aminotransferase (alanine: glyoxylate-aminotransferase AGT enzyme) OR
  - Oxidized to oxalate.



- Deficiency of the liver peroxisomal enzyme AGT causes overproduction of oxalate, and the formation of calcium oxalate kidney stones (Primary hyperoxaluria).



=====Thank You =====

=====Dr/ Marwa Dahpy =====